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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/989,695
Filing Date: November 20, 2001
Appellant(s): LOPEZ-BERESTEIN ET AL.

Monica A De La Paz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1-21-05.

RD

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Upon consideration, the 112, First paragraph rejection based on the written description requirements is withdrawn.

(7) Grouping of Claims

The rejection of claims 1-2 and 4-32 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,369,119	HERMANN et al	11-1994
5,435,989	PRESANT et al	7-1995
WO 99/00120	ARIZONA BOARD OF REGENTS, UNI. OF ARIZONA	1-1999

Sugarman, S. M., et al. "Liposomes in the treatment of Malignancy: a clinical perspective". Critical Reviews in Oncology Hematology. Elsevier Science Publishers. Vol. 12, 1992, pp. 231-242.

Ranade, V. V., "Drug Delivery Systems. 1. Site-Specific Drug Delivery Using Liposomes as carriers", J. Clin Pharmacol. vol. 29, 1989, pp. 685-694.

Mayer, L. D., et al. "Comparison of free and liposome encapsulated doxorubicin tumor drug uptake and antitumor efficacy in the SC 115 murine mammary tumor", Cancer Letters, vol. 53, 1990, pp. 183-190.

Weiner, N., et al, "Liposomes as a drug delivery system", Drug Development And Industrial Pharmacy, vol. 15, no. 16, 1989, pp. 1523-1554.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermann (5,369,119), further in view of either of the references of Sugarman et al (Critical Reviews in Oncology Hematology, 1992 or Ranade (J. Clin Pharmacol. 1989 or Mayer et al (Cancer Letters, 1990) or Weiner et al (Drug development and Industrial Pharmacy, 1989).

Hermann discloses compositions containing imexon and a lipid (magnesium stearate) (Example 7). On col. 2, line 58 et seq., Hermann teaches also the use of imexon in combination with other anti-cancer agents.

What are lacking in Hermann are the teachings of the use of liposomes as carriers for imexon and derivatives of imexon.

Sugarman while reviewing the use of liposomes as carriers of drugs in the treatment of malignancy teaches that liposomes are sustained release agents and the advantages of their use as carriers of drugs include reduced toxicity associated with those drugs. Sugarman also teaches the use of DMPC/DMPG in a ratio of 7:3. Sugarman further teaches that attachment of monoclonal antibodies to the surface of liposomes to direct the liposomes to the target tissue is known in the art (see entire publication, Introduction and Rationale in particular).

Ranade similarly discloses the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (pages 685-691).

Mayer et al teach the tumor uptake and anti-tumor efficacy of doxorubicin against murine mammary tumors (note the summary).

Weiner et al similarly teach the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (note Introduction and page 1553).

The use of liposomes as carriers for imexon would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer et al and Weiner et al. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes as also evident from Sugarman. The use of derivatives of imexon would have been obvious to one of ordinary skill in the art since active skeleton is the cyanoaziridine structures and therefore, one would expect at least similar results obtained using imexon.

Note: claim 2 is included in the rejection since liposomes are also called micelles as noted from Presant (5,435,989), which is cited of interest.

Appellant's arguments have been fully considered, but are not found to be persuasive. Appellant argues that one of the elements that is required for a prima facie case of obviousness to exist is that there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Hermann in view of either Sugarman, Ranade, Mayer, and Weiner and that none of the references make any suggestion of delivering imexon via administration of liposomes. These arguments are not found to be persuasive. As recognized by applicant himself there should be a

motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings. In instant case there is a clear motivation in the secondary references for one of ordinary skill in the art to use liposomes for the delivery of imexon. Sugarman, and Ranade in particular teach the advantages of using liposomes as sustained delivery agents for both hydrophobic and hydrophilic active agents, cancer agents in particular, and that of Mayer shows the increased uptake of the liposomes containing an anti-cancer drug by the tumor cells. Furthermore, liposomal art is well advanced in the sustained delivery of a variety of drugs and therefore, motivation to use liposomes comes from the knowledge available to one of ordinary skill in the art. Appellant argues that none of the drugs mentioned in the references have any similarity or structural resemblance to imexon and that hundreds of drugs exist for treating cancer such that one skilled in the art could not possibly know that imexon would be a drug appropriate for liposome delivery. This argument is not found to be persuasive since the novelty is the sustained delivery nature of the liposomes themselves and this sustained delivery does not depend upon the drug encapsulated and therefore, one of ordinary skill in the art would expect at least the same results using imexon as the drug. In this regard, the examiner respectfully directs board's attention to Weiner's statements on page 1528 that many liposome based pharmaceutical products are entering the clinical stage of development and several may reach the market place. This implies, many drugs have past the stages of both in vitro and in vivo studies using animal models and therefore, one of ordinary skill in the art would expect a reasonable success even with imexon. Appellant's

arguments that the prior art presents an 'obvious to try' situation are not persuasive since as pointed out above, the references of Sugarman, and Ranade are suggestive of the applicability of liposomal systems to both hydrophobic and hydrophilic active agents, cancer agent in particular. It is interesting to note that instant claim 1 recites just 'phospholipids' and includes even imexon derivatives. Based on applicant's own logic, just because liposomes are effective in the delivery of imexon, one cannot predict the same nature of the results with any imexon derivative (see claim 24 which recites several imexon derivatives) and phospholipids in a 'non-liposomal form'. Appellant's arguments based on apparent exceptionally superior activity against tumor cells are not persuasive. Appellant points out to examples 20 and 21 to show unexpected results. First of all, the experiments in Example 20 are in vitro experiments on specific cells, namely myeloma cells. Secondly, no statistical evaluation of the data has been done. A careful evaluation of Fig. 1 A indicates that actually the drug alone appears to be more cytotoxic than the liposomally encapsulated drug (see top curve). Similar is the case with data in Figures 1 B, 1 C, 2 A, 2 B and 2 C. With regard to the data in Example 21, these studies were performed with various derivatives of imexon and not using liposomal derivatives. It is the examiner's position that prima facie case of obviousness has been established. Instant specification contains no data at all to show the effectiveness of the liposomal imexon, let alone various derivatives of imexon claimed.

5. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/00120, further in view of either of the references of Sugarman et al (Critical Reviews in Oncology Hematology, 1992 or Ranade (J. Clin Pharmacol. 1989 or Mayer

et al (Cancer Letters, 1990) or Weiner et al (Drug development and Industrial Pharmacy, 1989).

WO discloses imexon and several of the claimed derivatives for treating cancer (abstract, pages 3-5). WO also teaches the use of imexon in combination with other anti-cancer agents (page 25). What is lacking in WO is the teaching of the use of liposomes as carriers for the delivery of imexon or its derivatives for the treatment of cancer or stimulating the immune system. It should be noted however that WO teaches the use of slow release carriers on page 22.

As pointed out above, Sugarman while reviewing the use of liposomes as carriers of drugs in the treatment of malignancy teaches that liposomes are sustained release agents and the advantages of their use as carriers of drugs include reduced toxicity associated with those drugs. Sugarman also teaches the use of DMPC/DMPG in a ratio of 7:3. Sugarman further teaches that attachment of monoclonal antibodies to the surface of liposomes to direct the liposomes to the target tissue is known in the art (see entire publication, Introduction and Rationale and Table 1 in particular).

Ranade similarly discloses the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (pages 685, 691).

Mayer et al teach the tumor uptake and anti-tumor efficacy of doxorubicin against murine mammary tumors (note the summary).

Weiner et al similarly teach the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (note Introduction and page 1553).

The use of liposomes as carriers for imexon or its derivatives taught by WO would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer et al, and Weiner et al. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes as also evident from Sugarman.

Note: claim 2 is included in the rejection since liposomes are also called micelles as noted from Presant (5,435,989), which is cited of interest.

Appellant's arguments have been fully considered, but are not found to be persuasive. Most of appellant's arguments are similar to those raised for the above 103 rejection and therefore, the same response is deemed applicable. Appellant in addition argues on page 19 of the brief that combining cancer drug therapies us highly unpredictable art and that trial and error is often required to determine the proper combination of therapies. The examiner agrees; however, this argument is not applicable in this instance since instant specification contains no in vivo data at all on imexon itself, let alone imexon (or its derivatives) in combination with other anti-cancer drugs.

6. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermann or WO cited above, in view of Presant (5,435,989).

The teachings of Hermann and WO have been discusses above. What is lacking in these references is the teaching of the use of phospholipid micelles or liposomes.

Presant teaches that when micellar particles such as liposomes containing active agents are injected into the host, there is an enhanced retention of the active agent in the tumor cells (abstract, col. 3, line 13 through col. 9, line 21 and claims).

The use of micellar particles such as liposomes for the delivery of imexon taught by Hermann or WO would have been obvious to one of ordinary skill in the art since Presant shows enhanced accumulation of these particles at the tumor site. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid in specific ratios is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes. The specification shows no data to indicate the criticality. As pointed out above, the use of derivatives of imexon would have been obvious to one of ordinary skill in the art since active skeleton is the cyanoaziridine structures and therefore, one would expect at least similar results obtained using imexon.

Appellant's arguments have been fully considered, but are not found to be persuasive. Appellant's arguments to this rejection are similar as those put forward to the above rejections and hence same response is deemed applicable.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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GSK

April 25, 2005

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